BIOMAGNETISM

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Introduction

The science of *biomagnetism* refers to the measurement of magnetic fields produced by living organisms. These tiny magnetic fields are produced by naturally occurring electrical currents resulting from muscle contraction, or signal transmission in the nervous system, or by the magnetization of biological tissue. The first observation of biomagnetic activity in humans was the recording of the magnetic field produced by the electrical activity of the heart, or *magnetocardiogram*, by Baule and McFee in 1963 (1). In 1968, David Cohen (2) at the Massachusetts Institute of Technology reported the first measurement of the alpha rhythm of the human brain, demonstrating that it was possible to measure magnetic fields of biological origin that are only several hundred femtoTesla in magnitude (1 femtoTesla = 10^{-15} Tesla) – more than one million times smaller than the earth's magnetic field (approx. $5x10^{-5}$ Tesla). These early measurements were achieved using crude instruments consisting of inductance coils of 1 to 2 million windings in magnetically shielded enclosures and using extensive signal averaging. Instruments with increased sensitivity and performance based on the *superconducting quantum interference device,* or SQUID became available shortly after these pioneering measurements. The SQUID is a highly sensitive magnetic flux detector based on the properties of electrical currents flowing in superconducting circuits, as predicted by Nobel laureate Brian Josephson in 1962 (3). The SQUID was soon adapted for use in biomagnetic measurements (4) and by the early 1970s, measurements of the spontaneous activity of the human heart (5) and brain (6) had been achieved without the need for signal averaging using superconducting sensing coils coupled to SQUIDs immersed in cryogenic vessels containing liquid Helium. Thereafter, the field of biomagnetism continued to expand with the further development of SQUID based

instrumentation during the 1970s and 1980s. The introduction in 1992 of multi-channel biomagnetometers capable of simultaneous measurement of neuromagnetic activity from the entire the human brain (7, 8) has resulted in widespread interest in the field of *magnetoencephalography* or *MEG* as a new method of studying human brain function.

Biomagnetic measurements are considered to have a number of advantages over more traditional electrophysiological measurements of heart and brain activity, such as the electrocardiogram or electroencephalogram. One significant advantage is that propagation of magnetic fields through the body is less distorted by the varying conductivities of the overlying tissues in comparison to electrical potentials measured from the surface of the scalp or torso and can therefore provide a more precise localization of the underlying generators of these signals. In applications such as MEG and MCG, these measurements are completely passive and can be made repeatedly without posing any risk or harm to the patient. Also, biomagnetic signals are a more direct measure of the underlying currents in comparison to surface electrical recordings that measure volume conducted activity that must be subtracted from a reference potential at another location complicating the interpretation of the signal. In addition, magnetic measurements from multiple sites can be less time consuming since there is no need to affix electrodes to the surface of the body. As a result, biomagnetic measurements provide an accurate and non-invasive method for locating sources of electrical activity in the human body. The development of multi-channel MEG systems has dramatically increased the usefulness of this technology in clinical assessment and treatment of various brain disorders. This has resulted in the recognition of routine clinical procedures by health agencies in the United States for the use of MEG to map sensory areas of the brain or localize the origins of seizure activity prior to surgery. Clinical applications of MCG

have also been developed although to a lesser extent than MEG. This includes the assessment of coronary artery disease and other disorders affecting the propagation of electrical signals in the human heart. Another biomagnetic technique, known as *biosusceptometry*, involves measuring magnetized materials in the human body by measuring their moment as they are moved within a strong magnetic field. These measures can provide useful information regarding the concentration of ferromagnetic or strongly paramagnetic materials in various organs of the body, such as iron particles in the lung or iron containing proteins in the liver. In addition, novel biomagnetometer systems are now available for the assessment of fetal brain and heart function in utero, and may provide a new clinical tool for the assessment of fetal health. Currently, there are more than 100 multi-channel MEG systems worldwide and advanced magnetometer systems specialized for the measurement of magnetic signals from the heart, liver, lung, peripheral nervous system, as well as the fetal heart and fetal brain are currently being commercially developed. Although biomagnetism is still regarded as a relatively new field of science, new applications of biomagnetic measurements in basic research and clinical medicine are rapidly being developed, and may provide novel methods for the assessment and treatment of a variety of biological disorders. The following section reviews the current state of biomagnetic instrumentation and signal processing and its application to the measurement of human biological function.

Biomagnetic Instrumentation

SQUID sensors and electronics

The SQUID sensor is the heart of a biomagnetometer system and it provides high sensitivity detection of very small magnetic signals. The most popular types of SQUIDs are DC and RF SQUIDs, deriving their names from the method of their biasing. The modern commercial biomagnetometer instrumentation uses DC SQUIDs implemented in low temperature superconducting materials (usually Nb). In recent years, there has been significant progress in the development of high Tc SQUIDs, both DC and RF. These devices are usually constructed from $YBa_2Cu_3O_{7-x}$ ceramics. However, due to their poorer low frequency performance and difficulties with reproducible large volume manufacturing they are not yet suitable for large-scale applications. An excellent review of SQUID operation can be found in (9).

The RF SQUID was popular in the early days of superconducting magnetometry because they required only one Josephson junction. However, in majority of low Tc commercial applications, the RF SQUIDs have been displaced by DC SQUIDs due to their greater sensitivity, although in recent years, interest in RF SQUIDs has been renewed in connection with high Tc superconductivity. The operation of SQUIDs is illustrated in Fig. 1.a. The DC SQUID can be modeled as a superconducting ring interrupted by two resistively shunted Josephson junctions as in Fig. 1.a (10). The Josephson junctions are superconducting quantum mechanical devices which allow passage of currents with zero voltage, and when voltage is applied to them, they exhibit oscillations with a frequency to voltage constant of about 484 MHz/μV. The resistive

shunting causes the Josephson junctions to work in a non-hysteretic mode, which is necessary for low noise operation (9). An example of a thin film DC SQUID, consisting of a square washer and Josephson junctions near the outside edge is shown in Fig. 1.b (11, 12). The usual symbol used to represent a DC SQUID is shown in Fig. 1.c.

Insert Figure 1 about here

The SQUID ring (or washer) must be coupled to the external world and to the electronics which operates it, see Fig. 2.a. When the DC SQUID is current biased, its I-V characteristics is similar to that of a non-hysteretic Josephson junction and the critical current I_o is modulated by magnetic flux externally applied to the SQUID ring. The modulation amplitude is roughly equal to Φ_o/L (9), where Φ_o is the flux quantum with magnitude $\approx 2.07 \times 10^{-15}$ Wb and L is inductance of the SQUID ring. The critical current is maximum for applied flux $\Phi = n\Phi_o$ and minimum for $\Phi = (n + 1/2)\Phi_o$. For monotonically increasing flux the average SQUID voltage oscillates as in Fig. 2.d with period equal to 1 Φ_o. The SQUID transfer function is periodic (Fig. 2.d) and to linearise it, the SQUID is operated in a feedback loop as a null detector of magnetic flux (13). Most SQUID applications use analogue feedback loop whereby a modulating flux with $\pm 1/4\ \Phi_o$ amplitude is applied to the SQUID sensor through the feedback circuitry (Fig. 2a and b). The modulation, feedback signal, and the flux transformer output are superposed in the SQUID, amplified, and demodulated in a lock-in detector fashion. The demodulated output is integrated, amplified and fed back as a flux to the SQUID sensor to maintain its total input close to zero. The modulation

flux superposed on the DC SQUID transfer function is shown in Fig. 2.d and the modulation frequencies are typically several hundreds of kHz.

Insert Figure 2 about here

For satisfactory MEG operation the SQUID system must exhibit large dynamic range, excellent inter-channel matching, good linearity, and satisfactory slew rates. The analog feedback loop is not always adequate and the dynamic range can be extended by implementing digital integrator as shown in Fig. 2.c, and by utilizing the flux periodicity of the SQUID transfer function (14). The dynamic range extension works in the following manner: The loop is locked at a certain point on the SQUID transfer function and remains locked for the applied flux in the range of ±1 Φ_o, Fig. 2.d. When this range is exceeded, the loop lock is released and the locking point is shifted by 1 Φ_o along the transfer function. The flux transitions along the transfer function are counted and are merged with the signal from the digital integrator to yield 32 bit dynamic range. This "flux slipping" concept can also be implemented using 4-phase modulation (15), where the feedback loop jumps by $\Phi_o/2$ and can also provide compensation for the variation of SQUID inductance with the flux changes.

Flux transformers

The purpose of flux transformers is to couple the SQUID sensors to the measured signals and to increase the overall magnetic field sensitivity. The flux transformers are superconducting and

consist of one or more pickup coil(s) which are exposed to the measured fields. The pickup coil(s) are connected by twisted leads to a coupling coil that inductively couples the measured flux to the SQUID ring (as shown in Fig. 2.a). Because the flux transformers are superconducting, their gain is noiseless and their response is independent of frequency. The flux transformer pickup coil can have diverse configurations as shown in Fig. 3. A single loop of wire acts as a magnetometer and is sensitive to the magnetic field component perpendicular to its area, Figs .3.a and 3b. Two magnetometer loops can be combined with opposite orientation and connected by the same wire to the SQUID sensor. Such configuration is sensitive only to the magnetic field changes across the device dimension and is called a 1^{st}-order gradiometer, Figs .3.c to e. Similarly, 1^{st}-order gradiometers can be combined with opposing polarity to form 2^{nd}-order gradiometers, Figs. 3.f and 3g, and 2^{nd}-order gradiometers can be combined to form 3^{rd}-order gradiometers, Fig. 3.h. The flux transformers in Fig. 3 are called hardware flux transformers, because they are directly constructed in hardware by inter-connecting various coils.

Insert Figure 3 about here

The main types of flux transformers used in commercial practice as the primary sensors are magnetometers (Fig. 3.a), radial gradiometers (Fig. 3.c), and planar gradiometers (Fig. 3.d). These different sensor types will measure different spatial pattern of magnetic flux when placed over a current dipole as shown in Fig. 4. The radial magnetometer produces a field map with one maximum and one minimum, symmetrically located over the dipole with zero field measured directly above the dipole (Fig. 4.a). The radial gradiometer in Fig. 4.b produces similar

field pattern as the magnetometer, except that the pattern is spatially tighter since it subtracts two field patterns measured at different distances from the dipole. The planar gradiometer field patterns are quite different from that of the radial devices. If the two coils of the planar gradiometer are aligned perpendicular to the dipole, as in Fig. 4.c, the planar gradiometer exhibits a peak directly above the dipole; if the two coils were aligned parallel to the dipole, the planar gradiometer exhibits a weak, clover-leaf pattern. When two orthogonal planar gradiometers are positioned at the same location, their two independent components can determine orientation of the current dipole located directly under the gradiometers (16).

In the absence of noise there are no practical difference between these types of flux transformers. However in the presence of noise, the signal-to-noise ratios (SNR) can differ greatly, resulting in significant performance differences between devices. For MEG applications, the magnitude of both the detected brain signal and environmental noise increases non-linearly with increasing gradiometer baseline (distance between coils). Since the signal and noise functional dependencies on baseline are different, SNR exhibits a peak corresponding to an optimum baseline of about 3 cm to 8 cm for 1^{st} order radial gradiometers (17). Magnetometers can be thought of as gradiometers with very long baseline and are not optimal because they can be overly sensitive to environmental noise. Planar gradiometers have good SNR for shallow brain sources but are suboptimal for deeper sources due to their short baselines resulting in poor depth sensitivity. Too long a baseline can also result in greater sensitivity to noise sources arising from the body itself, such as the magnetic field of the heart that may then contaminate the MEG signal. A detailed comparison of gradiometer design and performance can be found in (17).

Insert Figure 4 about here

Noise cancellation

Introduction

Since biomagnetic measurements must be made in real world settings, the influence of noise on the measurements is a major concern in the design of biomagnetic instrumentation. Environmental noise affects biomagnetometer systems even when they are operated within shielded rooms. Environmental noise results from moving magnetic objects and currents (cars, trains, elevators, power lines, etc.). These noise sources are many orders of magnitude larger than signals of biomagnetic origin as shown in Fig. 5.a. Note also, that only SQUID magnetometers have sufficient sensitivity for measuring biomagnetic signals of interest (atomic magnetometers are not yet suitable for biomagnetic applications (18)). For MEG applications, the resolution or white noise level of the sensors should be much less than the 'noise' level of brain activity (approx. 30 $fT/Hz^{1/2}$). An example of background brain activity is shown in Fig. 5.b. Also, certain MEG signal interpretation methods require the white noise to be as low as possible, however the noise level cannot be made lower than the contribution of noise from the cryogenic vessel (dewar) itself. As a compromise, the majority of the existing MEG systems exhibit intrinsic noise levels of < 10 $fT/Hz^{1/2}$ (typically about 5 $fT/Hz^{1/2}$), yet are able to tolerate unwanted environmental noise many orders of magnitude greater.

Insert Figure 5 about here

Magnetic shielding

Magnetic shielding is the most straightforward, though most costly method for reduction of environmental noise. A variety of shielded rooms have been used for biomagnetic applications and their relative shielding performance is shown in Fig. 6. The simplest shielding is accomplished through eddy currents by using a thick layer of high-conductivity metal (19). Eddy current shielding is not effective at low frequencies and therefore shielded rooms utilize high-permeability μ-metal, which depending on the number of layers, can provide attenuation in the range from about 30 to about 10^5 (20-23). Low frequency attenuation of nearly 10^8 was demonstrated with a whole-body, high Tc superconducting shield (24).

Environmental noise can also be reduced by active shielding, which can be employed either in unshielded environments (25), or in combination with shielded rooms (23, 26, 27). Active shielding system consists of a reference magnetometer, feedback electronics, and a set of compensating coils. The references measure the environmental noise and provide a signal that is amplified and fed into the compensating coils to reduce the noise. In general, the active shielding reduces the magnetic field noise due to far field sources and is effective only for magnetometers with no noise cancellation, while it has only a small effect on 1^{st}-order gradiometers or magnetometers with noise cancellation. For higher-order gradiometers, active shielding actually degrades system performance since the active coils can produce higher-order gradients that are larger than that of the environmental noise.

Insert Figure 6 about here

Noise reduction using higher order gradients

Since hardware noise cancellation (shielding or active noise cancellation) is usually not sufficient, additional methods, implemented in software or firmware, are employed. These methods either incorporate information from additional reference sensors or operate directly on the primary sensors. The reference sensors are typically a combination of SQUID magnetometers and gradiometers and the noise is cancelled by synthesizing either higher-order gradiometers or adaptively minimizing noise. The principle of synthetic gradiometer operation is similar for all gradiometer orders, and the method is illustrated for 1st-order gradiometer synthesis in Fig. 7.a (28). The primary magnetometer detects the magnetic field component parallel to its coil normal, **p** (unit vector). The three reference magnetometers are orthogonal and their vector output, **r**, corresponds to the environmental field at the reference location, **r** ≈ **B**. Then if α_p is the primary magnetometer gain and α_r the reference gain (identical for all three references), the synthetic 1st-order gradiometer, $g^{(1)}$, can be derived as

$$g^{(1)} = m_p - \frac{\alpha_p}{\alpha_r}(\mathbf{p}\cdot\mathbf{r}) \approx \alpha_p \mathbf{p}\cdot\mathbf{G}\cdot\mathbf{b} \qquad (1)$$

where **b** is the gradiometer baseline (a vector connecting the primary sensor and the reference centers), and **G** is the 1st gradient tensor at the coordinate origin. Eq.1 states that the synthetic 1st-order gradiometer is a projection of the 1st gradient tensor to the primary magnetometer orientation, **p**, and the baseline, **b**. To synthesize a 2nd-order gradiometer, a primary hardware or synthetic 1st-order gradiometer and a tensor 1st gradient reference are used, Fig. 7.b. Similar to Eq.1, it can be shown that the synthetic 2nd-order gradiometer output is a projection of the 2nd gradient tensor to the coil orientation **p** and the 1st- and 2nd- order gradiometer baselines $\mathbf{b}_1$ and $\mathbf{b}_2$. Synthesis of 3rd-order and higher-order gradiometers is similar (28).

Insert Figure 7 about here

Adaptive methods can also be applied in addition to the synthetic gradiometers and can incorporate the same references as the gradiometers, but their coefficients are explicitly computed to minimize correlated noise (28). The advantage of synthesizing higher-order gradiometers is that their coefficients are universal, independent of the noise character or sensor orientation (29). In contrast, the coefficients determined to adaptively minimize background noise are not universal because they depend on the noise character and sensor orientations (29) and assume that the noise environment is unchanging.

The noise cancellation achieved by various methods is illustrated in Fig. 8. The upper trace (a) shows the magnetic field noise outside a shielded room and trace (b) shows the field noise after attenuation by the shielded room. The difference of the two slopes is due to the frequency

dependent eddy current shield that is part of the room. Hardware 1st-order radial gradiometers with 5 cm baseline reduce noise by nearly a factor of 100 (c) and a synthetic 3rd-order gradiometer (d) reduces the noise by almost another factor of 100. The low frequency environmental noise can further be reduced by adaptive method (e). The combination of all methods in Fig. 8 achieves attenuation of > 10^7 at low frequencies.

Additional noise reduction methods can be employed in systems with a large number of channels. The simplest method is spatial filtering using Signal Space Projection (SSP) (30-32), which projects out from the measurement the noise components oriented along specific spatial vectors in signal space. The method works best when the signal and noise subspaces are nearly orthogonal. Related to the SSP is the noise elimination by rotation in the signal space (33), which avoids loss of degrees of freedom encountered in SSP. These methods are discussed further in the Signal Interpretation section.

Insert Figure 8 about here

Cryogenics

The sensing elements of a biomagnetometer system (SQUIDs, flux transformers, and their interconnections) are superconducting and must be maintained at low temperatures. Since all commercial systems use low temperature superconductors, they must be operated at liquid He temperatures of 4.2 K. These temperatures can be achieved either with cryocoolers or by a

cryogenic bath in contact with the superconducting components. The cryocoolers are attractive because they eliminate the need for periodic refilling of the cryogenic container. However, because they contribute magnetic and EMI interference, vibrational noise, thermal fluctuations, and Johnson noise from metallic parts (34), they are not yet commonly used in MEG instrumentation. Present commercial biomagnetometer systems rely on cooling by liquid He bath in a non-magnetic vessel with an outer vacuum space also referred to as a dewar. An example of how the components may be organized within the dewar for an MEG system is shown in Fig. 9.a (35). The primary sensing flux transformers are positioned in the dewar helmet area. The reference system for the noise cancellation is positioned close to the primary sensors and the SQUIDs with their shields are located at some distance from the references, all immersed in liquid He or cold He gas. The dewar is a complex dynamic device which incorporates various form of thermal insulation, heat conduction, and radiation shielding, as shown Fig. 9.b. Most commercial MEG and MCG systems have reservoirs holding up to 100 liters of liquid He and can be operated for periods of several days before refilling. An excellent review of the issues associated with the dewar construction is presented in (34).

Insert Figure 9 about here

Biomagnetometer systems – Overview

Presently, the most common biomagnetometer systems are those designed for measurements of neuromagnetic activity arising from the human brain, or magnetoencephalography (MEG) systems. The current generation of these systems consists of helmet shaped multi-sensor arrays

capable of measuring activity simultaneously from the entire cerebrum. In contrast, multi-channel magnetocardiogram (MCG) systems consist of a flat array of radial or vector devices (36-41) or systems with smaller number of channels operating at liquid N_2 temperatures (42-47) for better placement over the chest directly above the heart. These flats array systems can also be placed over other areas of the body to measure peripheral nerve, gastrointestinal, or muscle activity. These systems can even be placed over the maternal abdomen to measure heart and brain activity of the fetus and a custom shaped multi-channel array specifically designed for fetal measurements has recently been introduced (35, 48).

MEG systems

A diagram of a generic MEG system is shown in Fig. 10. The SQUID sensors and their associated flux transformers are mounted within a liquid He dewar suspended in a movable gantry to allow for supine or seated patient position. The patient rests on an adjustable chair or a bed. At present, the majority of MEG installations use magnetically shielded rooms, however, progress is being made towards unshielded operation. MEG measurements are often complemented by simultaneous EEG measurements or peripheral measures of muscle activity or eye movement. In addition, most commercial MEG systems provide a three-dimensional head position monitoring system (using solenoids placed at anatomical landmarks on the head) in order to precisely co-register the head position with the location of the sensor array. All signals are pre-amplified and transmitted from the shielded room to a central workstation for real-time acquisition and monitoring of the magnetic signals. Most MEG installations have provisions for stimulus delivery in order to study brain responses to sensory stimulation and video and intercom

systems in order to interact with the patient from outside the shielded room. Multi-channel MEG systems are commercially available from a number of manufacturers (35, 49-52).

Insert Figure 10 about here

Biosusceptometers

A somewhat different system design is encountered in biomagnetometer systems used for the measurement of magnetic materials in the human body, such as iron content in the liver or magnetic contaminants in the lung. These instruments contain both SQUID sensing coils and a superconducting magnet operated in persistent mode. The system is suspended over the patient's body on a bed with a water bag placed between the patient and dewar to provide continuity of the diamagnetic properties of body tissue. Fig. 11 illustrates the layout of a biosusceptometer system for liver measurements with a patient in a supine position on a moveable bed. The patient is moved vertically relative to the SQUID gradiometer-magnet system and flux changes due to the susceptibility of the liver are monitored. These measures of magnetic moment can then be used to estimate the concentration of the paramagnetic compounds within the liver (53-55).

Insert Figure 11 about here

Signal interpretation

Biomagnetometers measure the distribution of magnetic field outside of the body. Although the observed field patterns provide some information about the underlying physiological activity, ideally one would like to invert the magnetic field and provide a detailed image of the current distribution within the body. Such inversion problems are non-unique and ill defined. The non-uniqueness is either physical (56) or mathematical due to being highly under-determined (i.e., there are many more sources than sensors). In order to determine the current distribution, it is necessary to provide additional information, constraints, or simplified mathematical models of the sources. The field of source modeling in both MEG and MCG has been an intensive area of study over the last 20 years. In the following section we shall review briefly various methods of source analysis as it is applied to MEG, although these methods apply to other biomagnetic measurements such as MCG, with the main difference being the physical geometry of the conductor volumes containing the sources. For detailed reviews of mathematical approaches used in biomagnetism see (57-60).

Neural origin of neuromagnetic fields

Magnetic fields of the brain measured by MEG are thought to arise primarily from synaptic activity in the gray matter of the neocortex, while action potentials in the underlying fiber tracts (white matter) have been shown to produce only poorly synchronized quadrupolar sources associated with weak fields (61, 62). Some subcortical structures have also been shown to produce weak yet measurable magnetic fields but are difficult to detect without extensive signal processing (63, 64). The generation of magnetic fields in the human brain is illustrated in Fig.

12. The neocortex contains a large number of elongated and vertically oriented pyramidal cells (Fig. 12.b) that in their resting state maintain a negative intracellular potential of about -70 mV. Excitatory (or inhibitory) synaptic input near the cell body or at the superficial apical dendrites results in a graded depolarization (or hyperpolarization) at either end of the cell (Fig. 12.b). This results in current flow inside the cell that is roughly perpendicular to the cortical surface, called impressed or intracellular current and extracellular (return) currents that flow through the extracellular space in the opposite direction. Synchronous activation of asymmetrical pyramidal cells that produces sink and source patterns through the depth of the cortex is thought to be the main generator of cortical potentials in the EEG (65) and is the most likely candidate for the generation of magnetic fields. However, other types of cortical neurons may produce magnetic fields if depolarized asymmetrically.

Estimates of the extent of cortical activation typically measured by MEG vary. Current densities in the cortex have been estimated to be on the order of 50 pA-m/mm^2 (66) suggesting that cortical areas of at least 20 mm^2 must be activated in order to produce a sufficiently large external field to be observed by MEG (57, 59). However, current densities as high as 1000 pA-m/mm^2 have been recorded in vitro (67) indicating that much smaller areas of activation may be recorded magnetically. In addition, activation of various regions of the enfolded cortical surface – the gyri and sulci – will result in current flow that is either radial or tangential to the scalp surface, respectively (Fig. 12.c). If the brain is modeled as a spherical conducting volume, then due to symmetry, only the tangential currents will produce fields outside the sphere (68) (Figs.12.d, and e). In practice however, it has been shown that MEG may be insensitive only to a relatively small percentage of the total cortical area (69). If the magnetometer coils are placed

radial to the head surface, then MEG measures primarily the intracellular currents. In contrast, EEG recordings are primarily sensitive to the return volume currents (dotted lines in Fig. 12.d and e). Accordingly, the pattern of electrical potential over the scalp due to a current dipole has been shown to be orthogonal to the magnetic field pattern, and corresponds to the return volume current flow in the opposite direction than that of the impressed intracellular current (70, 71). The neurophysiological mechanisms of MEG signal generation have been confirmed in a number of in vitro studies by Okada and colleagues, using small array SQUID systems to measure magnetic fields in the turtle cerebellum and hippocampal slice preparations. A recent review of this work is presented in (72).

Insert Figure 12 about here

Equivalent current dipoles

The equivalent current dipole or ECD (68, 73) is the oldest and most frequently used model for brain source activity. It is based on the assumption that activation of a specific cortical region observed with MEG involves populations of functionally interconnected neurons (macrocolumns) within a small area. This localized population activity can be modeled by a vector sum or "equivalent" current dipole in a spherical conducting volume, since the head is approximately spherical in shape. ECD analysis proceeds by estimating a priori the number of dipoles and their approximate locations, and then adjusting the dipole parameters (location and orientation) by a nonlinear search that minimizes differences between the field computed from

the dipole model and the measured field (Fig. 13). This can be done at one time sample, or it can be extended to a time segment, where several dipoles are assumed to have fixed positions in space but variable amplitude. Such models are referred to as 'spatio-temporal' dipole models (74). The dipole fit procedures require the calculation of the magnetic field produced by a current dipole at each sensor – also termed the *forward solution*. Since the frequency range of interest for biomagnetic fields is below 1 kHz, the quasi-static approximations of Maxwell's equations apply. If the head is represented by a uniformly conducting sphere, then the radial magnetic field of an ECD, **q**, is given by the radial component of the well-known Biot-Savart law, $B_{rad}(\mathbf{r}) = \mathbf{B}(\mathbf{r}) \cdot \mathbf{r} / |\mathbf{r}|$, where the Biot-Savart vector field, **B**(**r**), is given by

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \frac{\mathbf{q} \times (\mathbf{r} - \mathbf{r}_o)}{|\mathbf{r} - \mathbf{r}_o|^3} \qquad (2)$$

where $\mathbf{r}_o$ is the ECD position and **r** is the position where the field is measured. For multiple ECDs or continuously distributed sources Eq.2 will also include the sum over all sources or the integral over the volume of the conducting sphere.

Generally, the vector of the external magnetic field is produced by both the primary current density reflecting the impressed (intracellular) currents, and volume currents that produce 'secondary sources' on the surface of the volume conductor. For complex shapes the calculation of the external field also requires knowledge of the conductivity profile of the conducting volume. The assumption of spherical symmetry however, simplifies the calculation, and the vector field **B(r)** due to a current dipole **q** in a sphere at location $\mathbf{r}_o$ (Fig. 13.b) is given by Sarvas (68) as:

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_o}{4\pi F^2}\left\{F\mathbf{q}\times\mathbf{r}_o - \left[(\mathbf{q}\times\mathbf{r}_o)\cdot\mathbf{r}\right]\nabla F\right\} \quad (3.a)$$

where

$$F = a\left(r\,a + r^2 - \mathbf{r}_o\cdot\mathbf{r}\right) \text{ and} \quad (3.b)$$

$$\nabla F = \left(r^{-1}a^2 + a^{-1}\mathbf{a}\cdot\mathbf{r} + 2a + 2r\right)\mathbf{r} - \left(a + 2r + a^{-1}\mathbf{a}\cdot\mathbf{r}\right)\mathbf{r}_o \quad (3.c)$$

and $\mathbf{a} = \mathbf{r} - \mathbf{r}_o$, $a = |\mathbf{a}|$, $r = |\mathbf{r}|$ and the permeability of free space $\mu_0 = 4\pi\times10^{-7}$H/m. The sensing coil measures the component of the vector field **B(r)** perpendicular to its surface area as shown Fig. 13.b. If the field is measured only in the radial direction, Eq. 3 simplifies to the radial component of the Biot-Savart law (Eq.2), and the volume currents do not contribute any field. It can be seen from Fig. 13 that the definition of the origin of the theoretical sphere relative to the head will influence the calculation of the external magnetic field and thus plays a significant role in the accuracy of the single sphere approach. Improved accuracy of the forward solution can be achieved by using more realistic models of the conducting surfaces and boundary element methods for the calculation of the magnetic field (60), but these methods are more computationally demanding. A simple improvement over the single sphere model can be achieved by using a multiple-sphere model, where independent spheres are determined for each sensor by evaluating local head curvature in the sensor vicinity (75).

Insert Figure 13 about here

The ECD procedure is very sensitive to the SNR and DC offsets and therefore works best when applied to averaged brain responses that are well time-locked to a sensory or motor event and requires an accurate estimate of signal baseline (e.g., pre-stimulus activity). This approach has proven useful for modeling simple patterns of focal brain activity, yet is compromised by interaction or "cross-talk" between simultaneously active sources, requiring that the number of dipoles be correctly specified. Also, ECD models do not correctly describe spatially "extended" sources – areas of cortical activity that may extend over an area of several cm^2.

Minimum norm

The dipole model assumes that the brain activity is localized in one or several small areas of the brain. Sometimes it is required to obtain a more general solution without an a priori assumption about the source distribution. This can be obtained by minimum norm methods, first proposed for MEG by Hämäläinen and Ilmoniemi (73). This inverse problem is under-determined, solutions are diffuse, and, un-weighted minimum norm favors solutions close to the sensors. The minimum norm method has also been adapted to produce more localized solutions. The algorithm, FOCal Undetermined System Solution (FOCUSS) utilizes a recursive linear estimation based on weighted pseudo-inverse solution (76) and the Minimum Current Estimate (MCE) utilizes the L1-norm approach (77). A related method, Magnetic Field Tomography

(MFT) (78) utilizes weights and regularization parameter which are optimized according to the given experimental geometry and noise. Another minimum norm based method is the algorithm LORETA (LOw Resolution Electromagnetic TomogrAphy) (79). This algorithm introduces a spatial second derivative operator (Laplacian) into the weighting function and seeks the minimum norm solution subject to the maximum smoothness condition. This requirement is justified on physiological basis by assuming that neighboring points in the brain are likely to be synchronized. The method produces low spatial resolution that is a consequence of the smoothness constraint. Methods based on simulated (surrogate) data have also been proposed for producing distributed, unbiased solutions based on the minimum-norm (80).

Bayesian inference

Bayesian inference has also been applied to the biomagnetic inverse problem, using probability distributions of many possible source solutions. This approach can easily incorporate a priori information that may influence the likelihood of features of the current distribution based on anatomy, maximum current strength, smoothness and so on (81, 82). This method determines expectation and variance of the a posteriori source current probability distribution given source prior probability distribution and data set (83, 84). The model can include probability weightings determined from other imaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) to influence the MEG current images.

Signal space projection

The Signal Space Projection (SSP) (31, 32) algorithm is an analysis method where the measured fields are expressed in terms of vectors in a M-dimensional signal space where M is the number of channels. It is assumed that component vectors corresponding to different neuronal sources have distinct and stable (fixed) directions in signal space, and only their magnitudes are functions of time. If the vectors are defined by modeling the field produced by known dipole sources, SSP can be used as a spatial filter that passes only signals corresponding to these known sources. Thus, we can define the output of a spatial filter as $y_\theta(t) = \mathbf{P}_\parallel \mathbf{m}(t)$, where $\mathbf{P}_\parallel$ is the parallel projection operator (84) constructed from the forward solutions of the dipole source(s) of interest, and **m**(t) represents a vector of instantaneous MEG measurement at time t. The output of the spatial filter then provides a time series that is the estimate of changing strength of the dipole source(s) over time. Alternately, if the vectors associated with artifact patterns are known, SSP can be used to remove these artifacts from the signal using orthogonal projection operators (30). If the signal vectors are determined from patterns in the data, the source model need not even be known. Note that restricting all sources to current dipoles in a known volume conductor model reduces SSP to the multiple dipole approximation (32).

Beamformers

The SSP method does not separate well sources that are not in orthogonal subspaces. To overcome this limitation, source analysis can be done by beamforming (borrowed from radio-communication and radar work). Beamformers utilize spatial and temporal correlations to obtain information about uncorrelated dipolar sources. The Linearly Constrained Minimum Variance (LCMV) beamformer in the form now used in MEG analysis was first described in 1972 (85) and can be used without specific information about source orientation. An introduction to the

beamformers may be found in (86) and a relatively recent review of various beamforming techniques in (87). As in the case of SSP, if vector **m**(t) represent an instantaneous MEG measurement in M-dimensional space, we can define a spatial filter centered on the location '**θ**' as $y_\theta(t) = \mathbf{W}_\theta^T \mathbf{m}(t)$, where $\mathbf{W}_\theta$ is a weight matrix. Only tangential sources contribute to the MEG signal. They can be decomposed into two orthogonal tangential directions and the corresponding forward solutions, $\mathbf{B}_{\theta 1}$ and $\mathbf{B}_{\theta 2}$, can be arranged in a forward solution matrix as $\mathbf{H}_\theta = [\mathbf{B}_{\theta 1}, \mathbf{B}_{\theta 2}]$. The beamformer weights are determined by minimizing the power projected from the location θ, $P_\theta = \mathbf{W}_\theta^T \mathbf{C} \mathbf{W}_\theta$, subject to the unity gain condition, $\mathbf{W}_\theta^T \mathbf{H}_\theta = \mathbf{I}$, where **C** is the covariance matrix of the measurement and **I** is the identity matrix. The weights are given as (88)

$$\mathbf{W}_\theta = \mathbf{C}^{-1}\mathbf{H}_\theta \left(\mathbf{H}_\theta^T \mathbf{C}^{-1} \mathbf{H}_\theta\right)^{-1} \qquad (4)$$

An alternative approach known as synthetic aperture magnetometry (SAM) defines an optimal dipole orientation for each spatial filter location (89). Only one vector is retained, $\mathbf{H}_\theta = \mathbf{B}_\theta$ simplifying Eq. 4 to $\mathbf{W}_\theta = \mathbf{C}^{-1}\mathbf{B}_\theta \left(\mathbf{B}_\theta^T \mathbf{C}^{-1} \mathbf{B}_\theta\right)^{-1}$. This approach produces higher spatial resolution due to less projected sensor noise by the spatial filter (90). The beamformer weights can be used to compute the time course of the dipole magnitude variation or power at a single location in the brain independently of other active sources, provided sources are not highly correlated. An especially useful quantity is the normalized power $Z_\theta = P_\theta / N_\theta$, where $N_\theta = \mathbf{W}_\theta^T \Sigma \mathbf{W}_\theta$ is the sensor noise projected by the beamformer from location 'θ', and Σ is the sensor noise covariance matrix (88). In contrast to P_θ and N_θ, the parameter Z_θ behaves gracefully through the center of the model sphere and does not exhibit a singularity. A spatial image of brain activity can be

obtained by computing the normalized power at individual brain voxels, θ, one at a time over a region of interest.

Multiple signal classification

MUltiple SIgnal Classification (MUSIC) is a signal space scanning method and is related to beamforming (91, 92). MUSIC requires an initial nonlinear step of partitioning the data covariance matrix into signal and noise subspaces using standard eigendecomposition methods. This partitioning can be more readily determined from the averaged data and as a result the method is more difficult to apply to spontaneous brain activity. Sources are located by scanning of the brain volume and at each location requiring that the dipole forward solution be orthogonal to the noise subspace (or parallel to the signal subspace). A more recent implementation known as recursively applied and projected MUSIC (RAP-MUSIC) projects out each located source and then repeats the scanning procedure (93). Similar to beamforming, MUSIC also assumes that there are fewer sources than sensors, the sources are uncorrelated and the noise is white. In the limit of high SNR (e.g., averaged data), a small number of sources, and white noise, the MUSIC localizer function and beamformer based source power estimates differ only by a scaling factor.

Independent component analysis

Independent Component Analysis (ICA) is a relatively new technique that allows separation of sources that are linearly mixed at the sensors. The method is also called blind source separation, because the source signals are not directly observed and nothing is known about their mixture (94, 95). The mixing model used for the separation is usually stated as $\mathbf{m}(t) = \mathbf{A}\mathbf{s}(t)$, where $\mathbf{m}(t)$ is the instantaneous vector of the measurement, $\mathbf{s}(t)$ is the instantaneous source activity vector,

and **A** is the mixing matrix. The procedure provides solution for an un-mixing matrix **B**, such that the estimated source activity is given as $\hat{\mathbf{s}}(t) = \mathbf{B}\mathbf{m}(t)$, where $\hat{\mathbf{s}}$ is the estimate of the source vector **s**. The sources are assumed to be statistically independent and the separation is obtained by optimizing a contrast function, that is a scalar measure of some distributional property of the output $\hat{\mathbf{s}}$. The contrast functions are based on entropy, mutual independence, high order de-correlations, and so forth. ICA has been applied to MEG and EEG to either remove artifacts or extract desired signals (96, 97).

Applications of Biomagnetic Measurements

Magnetoencephalography – Basic Studies

The most prevalent and rapidly growing application of biomagnetism is the field of magnetoencephalography (MEG) – the measurement of human brain activity. This field of basic and clinical research is also referred to as *neuromagnetism* or *magnetic source imaging* (98-100). The latter term is often used to refer to the localization of neural sources with respect to individual brain anatomy by the combination of MEG source modeling with structural imaging techniques such as magnetic resonance imaging (MRI). As noted in the introduction, the first magnetic fields recorded from the human brain involved the observation of spontaneous alpha rhythm activity. This was soon followed by the application of MEG measurements to the study of *evoked responses* of the human brain – time-averaged responses to discrete sensory or motor events that provide sufficient SNR to allow for the localization of brain regions contributing to the externally measured field patterns. Present MEG practice includes measurement of both evoked and spontaneous signals and is used for clinical purposes and for investigation of a wide range of brain processes.

Somatosensory evoked fields

Evoked responses to stimulation of the human somatosensory system (somatosensory evoked fields or SEFs) were first reported by Brenner and colleagues in 1987 (101). The observed magnetic brain response to electrical stimulation of the digit was of great interest since it demonstrated a well-characterized dipolar field pattern over the scalp indicative of a single neural generator located in the underlying somatosensory cortex. Subsequent studies have

shown that early components of the SEF occurring at latencies of 20 – 50 ms reflect early activation of the primary somatosensory cortex contralateral to the side of stimulation, and are generally well modeled as single ECD source in these brain regions (see (102) for a recent review). The earliest component at a post-stimulus latency of 20 ms (sometimes referred to as the 'M20' or 'N20m' since it is considered the magnetic equivalent of the negative N20 potential measured in the EEG) arises from the posterior bank of the central sulcus -- a primary somatosensory projection area. By stimulating different body parts, it can be shown that the N20m source reflects the somatotopic or "homuncular" organization of the ascending neural pathways of the somatosensory system to this brain region (103). Fig. 14 shows a typical SEF response to stimulation of the median nerve at the wrist and the localization of an ECD model fit to the N20m source in the corresponding somatosensory cortex.

Insert Figure 14 -- SEF map and dipole on MRI

When using extensive signal averaging, MEG recordings also reveal low-amplitude high-frequency oscillations in the 300 Hz to 900 Hz range during the period of the N20m response. Although their origin is still under debate, these oscillations have been proposed to reflect the activity of inhibitory interneurons in the somatosensory cortex (104). The N20m is followed by reversals of the same pattern at latencies of 30 and 40 ms that appear to reflect additional activation of somatosensory areas. These are followed by more complex and widespread activity from about 80 – 150 ms after stimulation that reflects bilateral activation of secondary somatosensory areas in the parietal operculum and is most likely related to higher order

processing of somatosensory input (105). MEG responses at latencies of 50 –70 ms are elicited by mechanical stimulation of the digits (106) and reflect somatotopically organized sources in the primary somatosensory cortex (71). A number of MEG studies have used mechanical SEFs to demonstrate functional reorganization or 'plasticity' of the somatosensory cortex resulting from anesthetic block or damage to the peripheral nerves or amputation (107), or even as the result of musical training (108).

Movement related fields

The first recordings of magnetic fields accompanying simple finger movements were reported in the early 1980's. Deecke and colleagues (109) observed slow magnetic field changes over sensorimotor areas of the brain preceding voluntary movements of the digits. These 'readiness fields' begin approximately a half a second prior to the onset of a voluntary movement and are thought to represent activation of brain areas involved in motor preparation (110). Dipole source analysis suggests that pre-movement fields arise primarily from bilateral activation of the primary motor cortex (even for unilateral movements) with larger amplitude fields and dipole magnitudes the contralateral to the side of movement (111).

Movement-evoked fields (MEFs) accompany the onset and execution phase of simple movements. The first component (MEFI) is the largest in amplitude and begins approximately 100 ms after onset of EMG activity in the involved muscles. These responses appear to arise from sources in the postcentral gyrus, most likely reflecting sensory feedback to cortex from proprioceptors in the muscles (112) and are correlated with movement velocity (113). Movements made in response to a sensory cue show a very similar pattern of activity, but with a

shorter latency of onset of pre-movement activity (114). Passive movements also elicit magnetic responses thought to reflect activation of the proprioceptive inputs to areas of the postcentral gyrus (115). MEG mapping studies have demonstrated activity in motor cortex during motor imagery providing evidence of the involvement of these brain areas in the simple imagination of movement (116).

MEG-EMG Coherence

Using a single channel magnetometer, Conway and colleagues (117) made the interesting observation of increased coherence (correlation in the frequency domain) between the surface electromyogram (EMG) in a contracting muscle and MEG recordings made over the contralateral motor areas. Subsequently there has been a great deal of interest in the relationship between MEG-EMG coherence and the functional relationship between spontaneous cortical rhythms and EMG activity during movement (118). Interestingly, changes in the frequency of coherence varies with the strength of muscular contraction and recent studies have shown that MEG-EMG coherence may reflect the underlying physiology of tremor in patients with Parkinson's disease (119) or essential tremor (120).

Sensorimotor rhythms

MEG studies have also provided evidence for the functional significance of specific oscillatory brain activity in humans associated with both somatosensory stimulation and motor output. These centrally distributed rhythms were first observed in the EEG, and are predominant at frequencies around 10 Hz (also referred to as the mu rhythm) and in the range of 20-30 Hz.

MEG studies have been able to show that these are functionally independent cortical oscillations that originate from postcentral and precentral regions, respectively (121, 122). These sensorimotor rhythms are suppressed during median nerve stimulation, followed by a transient increase or 'rebound' of 20-30 Hz rhythms within 500 ms after stimulus onset. A similar pattern of suppression followed by rebound is observed during voluntary movements (123). These rhythmic changes are modulated by sensorimotor tasks such as movement or passive tactile stimulation and motor imagery or even observation of another individual's movements (121). Rhythmic activity is not amenable to the same signal averaging technique used for evoked fields and therefore the ECD source modeling approach is more difficult to apply. Spatial filtering methods such as beamforming however, provide a new method for the localization of frequency dependent power changes in cortical areas using MEG and have been applied to the localization of rhythmic changes induced by somatosensory stimulation (124) and voluntary movements of the digits (125).

Insert Figure 15

Visual evoked fields

One of the first magnetic evoked responses recorded from the human brain was the visual evoked field or VEF reported by Brenner and colleagues in 1975 (126). Robust responses can be elicited at latencies of 100 to 150 ms following visual stimulation using light flashes or visual pattern contrast changes (e.g., reversing checkerboard stimuli). However, early VEF responses pose a challenge in terms of modeling their sources due to the complex enfolded cross-like shape

of the primary (striate) visual cortex – also referred to as the 'cruciform' model. More recently, investigators have successfully modeled early VEF components in primary visual cortex by stimulating restricted portions of the total visual field using both monochrome (127) and color (128) pattern stimuli and have produced source configurations that reflect the retinotopic organization of the primary visual cortex. Due to the difficulty in applying ECD models to the VEF response, spatial filtering methods such as beamforming have been found to be useful for imaging visual cortex function (129). Fig. 15 shows the activation of primary visual cortex by a steady state visual pattern (reversing checkerboard) using the SAM beamforming algorithm. Visual stimuli also activate several non-primary (extrastriate) visual areas depending on the attributes of the stimulus. A number of MEG studies have shown activation of brain areas related to higher order visual processes such as detection of coherent motion (130, 131). Clinical applications of VEFs have been limited, although abnormal VEFs have been reported in cases of strabismic amblyopia (132).

Auditory evoked fields

Auditory evoked fields were first reported by Reite and colleagues (133) and subsequent MEG mapping studies have demonstrated that responses at latencies of 50 and 100 ms reflect activity of primary auditory cortex in the temporal lobes (134). The largest response occurring approximately 100 ms following stimulus onset, termed the M100, has been the most extensively studied auditory evoked field response. The M100 is bilateral for both binaural and monaural stimuli and has been shown to reflect the frequency specific (tonotopic) organization of the primary auditory cortex (135). These magnetic evoked responses are of interest in the study of the functional organization of the auditory system as they reflect perceptual attributes of auditory

stimulation such as perceived pitch or the frequency profiles of complex speech sounds (136, 137). Auditory responses to repetitive (steady-state) auditory stimuli show enhanced amplitude in the EEG at presentation rates of about 40 Hz and were initially thought to represent volume conducted thalamic responses. However, MEG steady-state auditory responses were shown by Weinberg and colleagues (138) to reflect oscillations at the stimulus frequency in the auditory cortex. Subsequent studies have suggested that 40 Hz auditory responses reflect thalamo-cortical networks in the brain responsible for integration of sensory input (139). The 40 Hz MEG response has recently been used to measure temporal integration times in the primary auditory cortex (140).

MEG studies of higher brain function

Although early MEG studies have provided useful information regarding the early processing of sensory input and motor output, one of the more intriguing potential uses of MEG is the non-invasive study of higher brain function. EEG studies of cognitive function have been carried out using event-related potentials (ERPs) for many decades. MEG measurements using similar paradigms have helped gain a better understanding of the neural basis of many ERP components. Early MEG studies have had some success in measuring brain responses related to short-term memory (141), target detection tasks (142) or selective attention (143). More recently, the use of whole head MEG systems have enabled the study of more complex aspects of cognitive processing in humans, such as face recognition (144) and object naming (145). Basic research on brain mechanisms related to speech and language is also a promising area of application for MEG. Early studies have shown that speech processing is affected by incongruous visual feedback at the level of the auditory cortex (146). Recent studies have attempted to localize

brain responses related to semantic processing, such as the recognition of incongruous words in sentences (147), and these MEG responses have been used to study abnormal processing of sensory input during reading in dyslexic children (148) and during speech in stutterers (149).

A great deal of progress has been made in studying higher brain function with MEG by applying traditional source analysis methods to ERP components. However, these complex brain processes often involve activation of multiple brain regions complicating the interpretation of the data in terms of simple ECD models. Moreover, many of these processes may not be highly time-locked to specific sensory or motor events. More recent approaches have focused on oscillatory brain activity and synchronization or 'phase-locking' between different cortical areas. Accordingly, this has produced increased interest in brain imaging methods with fine temporal resolution such as MEG. Rhythmic activity in the so-called gamma frequency band (30 – 90 Hz) is of particular interest since it is associated with cognitive processes such as feature binding within a sensory modality that may underlie perception (150). Recent studies have also described changes in neuromagnetic rhythms associated with observation and imitation of other individual's actions that appear to originate in brain areas associated with learning through imitation (151). Since changes in spontaneous brain rhythms are not necessarily time-locked to a stimulus onset, alternative signal processing techniques are required (152). The combination of spatial filtering source analysis methods and time-frequency and phase analysis may be particularly well suited to measure these aspects of higher order brain function (122) and constitute a new and interesting avenue of research in human cognition.

Magnetoencephalography - Clinical applications

Presurgical functional mapping

One of the more prevalent clinical applications of MEG is the localization of so-called 'eloquent cortex' – those areas that subserve sensory, motor, speech and memory function – prior to neurosurgery in order to prevent loss of these functions as a result of the surgical procedure. Due to displacement cortical tissue by space occupying lesions such as tumors, or natural variability in cortical morphology, identification of these brain areas may not be possible by visual inspection alone and can be aided by functional localization of these areas using MEG (99). This is achieved by activating primary sensory areas associated with visual, somatosensory and auditory stimulation and applying ECD models to the early evoked response – a method generally referred to as *presurgical functional mapping*. For example, the N20m source of the somatosensory evoked field can be consistently and reliably localized in most individuals and used as an estimate of the location of the central sulcus prior to surgical removal of brain tissue in the region of the primary motor or somatosensory cortex (153). Determination of the language dominant hemisphere is also necessary prior to surgical resection of cortical tissue near language areas of the temporal lobe. This is routinely done through highly invasive procedures such as selective anesthesia of the left and right hemispheres (*Wada test*) or direct cortical stimulation intra-operatively. The use of MEG for the localization of brain areas that are specific to the processing of speech, as distinct from areas associated with the simple processing of auditory input, constitutes a challenging area of research, however some recent progress has been made in this area (154). Presurgical mapping of cortical functional areas using MEG is of particular interest given its non-invasiveness and potential greater accuracy in comparison to other imaging methods such as function magnetic resonance imaging (100).

Epilepsy

Due to its high temporal resolution and ability to localize focal brain activity, there has been a long interest in the application of MEG to the study of epilepsy. In many case, intractable seizures can be controlled by the removal of the epileptogenic tissue. This may comprise an irritative zone around a structural lesion or some unidentified area of the brain from which seizure activity may originate. The localization of ECD sources based on MEG recordings of interictal ('between seizure') spiking activity has been shown to be highly correlated with the localization of the epileptogenic zone as identified by other methods such as direct intracranial monitoring from depth or subdural electrode grids (for recent reviews see (155-157)). Since interictal spikes are of very large magnitude, ECD models can be used to localize individual spike events without averaging. However since the spatial variability of these localizations is high, the aggregate locations of many spike sources are often used to estimate the putative brain area of seizure generation. Other methods, such as spatial filtering by beamformers (SAM), are currently being investigated and may help overcome some of the limitations of the single ECD approach to the localization of epileptogenic foci. Even in cases where the precise location of the epileptogenic zone is not identified, MEG may help guide the placement of subdural grids and in some cases may be used to evaluate the propagation of abnormal electrical activity between multiple brain regions. The diagnostic yield of MEG measurements of interictal activity varies with different forms of epilepsy and appears to be highest for neocortical epilepsy (158) and can also aid in the differentiation of different types of epilepsy (156).

Since the site of brain pathology may not be known in advance, particularly in nonlesional epilepsy, the introduction of whole-head MEG systems has drastically improved the feasibility of using MEG as a routine clinical procedure for presurgical epilepsy evaluation. The main drawbacks to the application of MEG in epilepsy is the inability to measure brain activity associated with seizure onset due to head movement, and the difficulty in performing long-term monitoring of interictal activity, although this is somewhat ameliorated by the introduction of MEG systems that allow recording from patients in the supine position and while asleep. As a result, the combination of standard clinical EEG methods and MEG source localization will probably provide the most useful diagnostic battery in the surgical treatment of epilepsy.

Pain Studies

MEG studies have focused on pain related brain responses by selectively stimulating the Aδ and C fiber systems painful CO_2 laser stimulation of the skin (159) or direct electrical stimulation of nerve fibers (160). This type of somatosensory stimulation produces long latency responses in secondary somatosensory areas located in the parietal operculum, and insula – brain regions known to be involved in the perception of pain. Such studies are promising for the clinical treatment of chronic pain, although are challenging due to the difficulty in discriminating activation of brain areas due to painful versus non-painful somatosensory input, and the invasiveness of the procedure.

Other clinical applications

Although presurgical functional mapping and epilepsy have been the main areas of clinical application of MEG, other brain disorders have been studied. This includes the use of MEG to study recovery after stroke due to functional reorganization of the cortex (161) and its relationship to rehabilitation and outcome (162) and the evaluation of patients with mild head injury (163). Low frequency neuromagnetic activity has been hypothesized to be an index of spreading cortical depression associated with migraine (164). Although still a new area of study, there is a great deal of interest in the application of MEG to psychiatric disorders. For example, MEG studies have reported abnormal auditory evoked magnetic fields in schizophrenic patients (165) and patients with Alzheimer's disease (166).

Magnetocardiography

The first biomagnetic measurements in humans were measurements of the magnetic field of the heart. The field of magnetocardiography or MCG has not expanded as rapidly as that of MEG, although a number of research centers have continued to develop the MCG method for the noninvasive evaluation of cardiac disease. As described in the Instrumentation section, MCG requires instrumentation designed for the adequate sampling of the heart's magnetic field over the chest and a number of instruments have been developed and installed at research centers around the world, including systems based on high temperature SQUIDs. Source modeling based on magnetic field measurements is somewhat simplified in the case of MEG due the ability to model the head as a spherically shaped conductor, whereas, modeling of the electrical activity of the heart requires realistic models of the conducting properties of the thorax and its

influence on the distribution of magnetic fields arising from the heart. As a result source localization methods in MCG often employ boundary element methods for forward calculations (167). Source localization in MCG is further complicated by the continuous movement of the heart itself. Nevertheless, MCG has been successfully used in the diagnosis of cardiac disease. For recent reviews see (168-170).

Since the 1980s a number of studies have focused on the use of MCG for the three-dimensional localization of the origins of abnormal electrical activity of the heart. This includes abnormal activity underlying cardiac arrhythmias, such as Wolff-Parkinson-White syndrome, which involves abnormal electrical activity (pre-excitation) in the accessory pathway. Recent studies have shown that MCG studies provide more accurate localization of the site of pathology than standard multichannel electrocardiogram techniques (171). The identification of the generators of heart arrhythmias is useful in presurgical evaluation for interventional procedures such as catheter ablation therapy, or in the screening of patients at risk for ventricular tachycardia (168) or coronary artery disease (172). Another application of MCG is in the assessment of ischemic areas of the heart after infarction by the detection of regions of low current density (173).

Fetal Studies

One of the more intriguing new applications of biomagnetism is the noninvasive measurement of activity of the fetal heart and brain. Since the first report of the detection of an evoked response from the fetal brain in 1985 (174) there has been a great of interest in developing instrumentation for the measurement of biomagnetic fields from the human fetus. The main challenges for the measurement of fetal MCG or MEG is the detection of biomagnetic sources that are distant from

the detector array, and the difficulty in establishing the position of the fetal heart and brain during measurement. The latter has been partially resolved by the combination of fetal biomagnetic measurements with three-dimensional ultasound imaging and new instrumentation has been recently designed for optimum placement and sensitivity of the sensory array to detect fetal heart and brain responses.

Fetal MCG

The largest biomagnetic signal arising from the fetus is the fetal magnetocardiogram or fMCG. The first recording of fMCG was demonstrated in 1984 (175). The fMCG signal magnitude is quite large, but due to proximity of the fetus to the mother's heart, signal processing methods are required to first remove the large maternal heart signal, after which the P, QRS, and T segments of the fMCG can be discerned with high reliability in fetuses beyond the 20th week of gestation (176). Fetal heart rate variability has been shown to be a good indicator of fetal well-being (177). This method has been applied to the detection of fetal arrhythmias (178) and may provide a useful diagnostic or screening tool for fetal congenital heart defects (179), or for the assessment of fetal health in high-risk pregnancies. An overview of fMCG can be found in (180).

Fetal MEG

Due to the distance of the fetal brain from the surface of the maternal abdomen, the fetal MEG (fMEG) signal is difficult to detect without high sensitivity biomagnetometer with large coverage, large number of channels, and optimal placement of the sensor array. In addition, the fetal brain signals are small in comparison with an adult and their measurement is performed in the presence of strong interference from the maternal and fetal heart signals and various

abdominal signals (intestinal electrical activity, uterine contractions, etc.). Measurements of fetal brain responses to sensory stimulation are also hampered by the difficulty in delivering the sensory stimulus to the fetus. However, fetal auditory evoked responses have been successfully recorded by presenting high amplitude auditory stimuli directly to the mother's abdomen (181, 182). In order to successfully eliminate the interference due to cardiac signals (which can be more than 100 times larger than the fMEG), the latter efforts employed various signal extraction methods (spatial filtering, PCA, and so forth) in addition to averaging. Magnitudes of fMEG responses to transient tone bursts are in the range of about 8 to 180 fT and the latencies range from about 125 to nearly 300 ms, decreasing with the increasing gestation age (183). The response is typically observed in not more than about 50% of examined subjects. The fetal responses to steady-state auditory clicks has also been reported (184).

Insert Figure 16

Early fMEG experiments used single or multiple-channel probes with relatively small area of coverage, requiring a search for the region with the largest signals. Recently, a dedicated fetal MEG system, the SQUID Array for Reproductive Assessment (SARA), was constructed and operated (48). The SARA system consists of an array of 151 SQUID sensors covering the mother's anterior abdominal surface in late gestation, from the perineum to the top of the uterus as shown in Fig. 16.a and b. The primary sensor flux transformers are axial 1^{st}-order gradiometers, with 8 cm baselines and the nominal SQUID sensor noise density is 4 $fT/Hz^{1/2}$. The SARA system is now being used routinely in a number of research centers and was recently

used to measure the first fetal visual evoked field to high intensity light stimuli presented to the maternal abdomen (185). An example of a flash evoked response from the fetal brain is shown in Fig .16.c.

Other Applications

Biosusceptometry

The greatest interest in biosusceptometry has stemmed from its potential to assess non-invasively iron overload in the human liver. This potentially fatal condition arises in individuals with hemoglobinopathies that require frequent blood transfusions (e.g., sickle cell anemia) or involve abnormal production of hemoglobin (hemachromatosis and beta-thalassemia). Standard methods for assessing iron overload can be highly invasive (e.g., liver biopsy) and biosusceptometry offers a safer and potentially more accurate diagnostic tool. Iron, which is normally strongly ferromagnetic, is stored in the liver bound by the proteins ferritin and hemosiderin and exhibits a strong paramagnetic response. As a result, measurement of the magnetic moment produced by placing the liver in a uniform magnetic field will be proportional to the total amount of iron in the liver – a method known as *biomagnetic liver susceptometry* (BLS). The basis for this technique was first proposed and the first measurements carried out in the late 1970s (186).

Most approaches to the measurement of hepatic iron concentration involve placing the patient's abdomen directly under a magnetic sensor that also contains a field coil that produces a weak magnetic field, and lowering the patient by a fixed distance to measure the change in field

amplitude due to the magnetized liver (Fig. 11). In order to eliminate the effect of the surrounding air, a water-filled bellows is placed between the abdomen and the device to simulate the diamagnetic properties of the other tissues in the body. The main challenge to accurate estimates of hepatic iron content using BLS is the remaining effect of the varying susceptibility of the lungs and air filled compartments in the abdomen. Since this technique requires the application of a DC magnetic field to the body on the order of about 0.1 Tesla, it is a much more invasive technology in comparison to MEG and MCG, and may be contraindicated in patients with implanted medical devices such as pacemakers. A detailed review of the clinical applications of BLS can be found in (187).

Peripheral nerve studies

It is known from the pioneering studies of Wikswo and colleagues (61) that the propagation of action potentials in nerve fibers produces quadrupolar like sources that have a rapidly diminishing magnetic field with distance. This is due to the fact that action potentials consist of a traveling wave of depolarization in the axon, followed closely by a wave of repolarization. In addition, due to varying conduction velocities in the peripheral nerves, action potentials in different axons will not necessarily summate to produce coherent synchronous activity. As a result, activation of compound nerve bundles does not produce coherent dipole-like sources as in the case of the neocortex. However, with sufficient signal averaging it is possible to record the magnetic signature of the sensory nerve action potentials non-invasively in the human – a technique referred to as *magnetoneurography*. These measures have been achieved by placing single channel magnetometers or flat arrays of magnetic sensors over the peripheral nerve pathways and electrically stimulating the nerve. The predicted quadrapolar pattern of traveling

actions potentials resulting from electrical stimulation of the finger was reported by Hoshiyama and colleagues using a 12 channel "micro-SQUID" device placed over the wrist (188). Mackert and colleagues, using a 49 channel flat triangular array of 1st order radial gradiometers were able to measure compound action potentials elicited by tibial nerve stimulation in sensory nerves entering the spinal cord at the lower lumbar region, and have recently using this method clinically to demonstrate impaired nerve conduction in the patients with S1 root compression (189).

Magnetopneumography

Magnetopneumography refers to the measurement of the remanent magnetism of ferromagnetic particles in the lungs. This technique may be used to assess lung contamination encountered in occupations that may involve the inhalation of ferromagnetic dust particles such as arc-welders, coalminers, asbestos, and foundry and steel workers. Similar to liver biosusceptometry, magnetopneumography involves the application of a weak DC magnetic field to the thorax. However, the field is applied for only a short interval in order to produce a remanent magnetization of ferromagnetic material, usually iron oxides such as magnetite. This remanent magnetic field is then measured to assess to total load of ferromagnetic particles in the lung. These measures can be used to evaluate the quantity and clearance rates of these substances (190, 191). A related measure is *relaxation* – the decay of the remanent field due to the re-orientation of the magnetic particles away from their aligned state after application of the DC field. Relaxation times are thought to reflect cellular processes in the lung associated with clearance or macrophage activity on the foreign particles. Recent studies have used magnetopneumography to study the effect of smoking on clearance times of inhaled magnetic particles (192).

Gastrointestinal system

Biomagnetic measurements have also been applied to other areas of the human body. The human gastrointestinal system produces electrical activity associated with the processes of peristalsis and digestion of food. For example, slow electrical activity at frequencies of about 3 cycles per minute (0.05 Hz) can be recorded from the human stomach using cutaneous surface electrodes or magnetically – a technique referred to as *magnetogastrography* (MGG). This activity arises from the smooth muscle of the stomach and the detection of changes in frequency with time has been proposed as a method of characterizing gastric disorders (193). Another novel application of biomagnetic instrumentation to gastrointestinal function, is the three-dimensional tracking of the transport of magnetic materials through the gut. This technique has been termed *magnetic marker monitoring* (MMM) and can be used to monitor the passage and disintegration (by measuring decrease in magnetic moment) of magnetically labeled pharmaceutical substances through the gastrointestinal system (194).

Future Directions

Since its inception 40 years ago with the first recording of the magnetic field of the heart, the field of biomagnetism has expanded immensely to become a major field of basic and applied research. The field of magnetoencephalography, or MEG, has in recent years become a recognized neuroimaging technique, with the development of advanced instruments for the measurement of the electrical activity of the brain with exquisite temporal and spatial resolution. Biomagnetic instrumentation is now at a mature state, with commercially developed

measurement systems available for a variety of biomagnetic applications. For example, whole head MEG systems are installed worldwide in over one hundred research laboratories and clinical centres and are now being used in routine clinical diagnostic procedures. Nevertheless, there remain many areas for further improvement of both instrumentation and data analysis approaches and techniques. In terms of instrumentation, biomagnetometer systems with increased number of sensing channels and capable of unshielded operation will likely be developed, and present systems which require frequent refilling with liquid Helium may be replaced by systems with longer hold times and less frequent cryogen replenishment. The latter may be accomplished either by incorporation of cryocoolers, or the use of sensors that do not require liquid He. The last two technical innovations, combined with production of larger numbers of MEG systems will also help reduce the cost of these instruments.

The analysis and interpretation of biomagnetic measurements is possibly the most significant area for continued research and development, and much progress has been made in the implementation of new signal processing algorithms for the extraction of biomagnetic signals, or improving the spatial resolution of source localization methods. There has been recent interest in combining MEG with its high temporal resolution and other functional imaging techniques, for example, functional MRI. In addition, advanced image processing techniques, such as the automated extraction of the cortical surface of the brain from structural MRI, will allow the use of more precise physical models of biomagnetic sources. Combination of MEG with its counterpart EEG may also help to develop more accurate models of brain activity. These advancements will aid the development of new clinical applications of biomagnetism such as the use of MEG to study psychiatric disorders, or to study the effects of drug treatments on brain

processes related to cognitive deficits, or gain insight into the physiological mechanisms underlying various brain disorders in children, for instance, learning disabilities, dyslexia and autism. Finally, novel applications of biomagnetic measurements, for example, the measurement of heart and brain activity in the fetus, will lead to new applications of biomagnetism in clinical medicine and will further drive the development of improved technology. In sum, biomagnetism will continue to grow as a novel and powerful non-invasive technique for the study of physiological processes in humans in both health and disease.

Figure Captions

Fig. 1. Thin film dc SQUID. (a) Schematic diagram indicating inductances of the SQUID ring and shunting resistors to produce non-hysteretic Josephson junctions; (b) Diagram of a simple SQUID washer with Josephson junctions near the outer edge; (c) Symbolic representation of a dc SQUID, where the Josephson junctions are indicated by 'x'. Reproduced with permission from (17).

Fig. 2: Examples of SQUID electronics, where the SQUID is operated as a null detector. (a) SQUID sensor is coupled to an amplifier; (b) Analog feedback loop; (c) Digital feedback loop using digital signal processor (DSP) or a programmable logic array (PGA); (d) Feedback loop modulation. Adapted with permission from (17).

Fig. 3: Examples of hardware flux transformers for biomagnetic applications. It is assumed that the scalp surface is at the bottom of the figure. (a) radial magnetometer; (b) Tangential magnetometer; (c) Radial 1^{st}-order gradiometer; (d) Planar 1^{st}-order gradiometer; (e) Radial gradiometer for tangential fields; (f) 2^{nd}-order symmetric gradiometer; (g) 2^{nd}-order asymmetric gradiometer; (h) 3^{rd}-order gradiometer. Reproduced with permission from (17).

Fig. 4: Response to a point dipole of several flux transformer types. A tangential dipole is positioned 2 cm deep in a semi-infinite conducting space bounded by $x_3 = 0$ plane and its field is scanned by a flux transformer with its sensing coil positioned at $x_3 = 0$. Dipole position is indicated by a black arrow. Dimensions of each map are 14 x 14 cm. Schematic top view of the

flux transformers is shown in the upper part of each figure. Solid and dashed lines indicate different field polarities. (a) Radial magnetometer; (b) Radial gradiometer with 4 cm baseline; (c) Planar gradiometer with 1.5 cm baseline aligned for maximum response; (d) Planar gradiometer with 1.5 cm baseline aligned for minimum response. Reproduced with permission from (17).

Fig. 5: Environmental and brain generated noise. (a) Comparison of biomagnetic fields, environmental noise, and sensitivity in 1 Hz bandwidth of various types of magnetometers; (b) Spontaneous brain activity and the system noise measured in an unshielded environment, noise cancellation by synthetic 3rd-order gradiometer, primary sensors are radial 1st-order gradiometers with 5 cm baseline. Control trace was collected with no subject in the helmet, large lines correspond to signals due to nearby rotating machinery, Eyes closed and open were collected with the subject in the MEG helmet. The presence of alpha activity (peak at 8 Hz) is visible in the eyes closed condition. Reproduced with permission from (29).

Fig. 6: Noise attenuation of various shielded rooms as a function of frequency. (a) Eddy current Al rooms; (b) Standard μ-metal rooms used for MEG applications; (c, d) High attenuation μ-metal rooms; (e) Combination of high attenuation m-metal room in 'd' and active shielding; (f) Whole-body high temperature superconducting shield. Adapted with permission from (29).

Fig. 7: An illustration of gradiometer synthesis. (a) Synthesis of a 1st-order gradiometer from a primary magnetometer sensor and a vector magnetometer reference; (b) Synthesis of a 2nd-order gradiometer from hardware 1st-order gradiometer and a 1st gradient tensor reference. Adapted with permission from (195).

Fig. 8: Reduction of environmental noise by a moderately shielded room, synthetic gradiometers, and adaptive methods. (a) Magnetic field noise outside a shielded room; (b) Field noise after attenuation by the shielded room; (c) Noise reduction by hardware 1^{st}-order gradiometer with 5 cm baseline; (d) Noise reduction by synthetic 3^{rd}-order gradiometer (nearly 4 orders of magnitude lower noise than that of a shielded magnetometer in 'b'); (e) Noise reduction by addition of adaptive methods to synthetic 3^{rd}-order gradiometer. Adapted with permission from (196).

Fig. 9: Schematic diagram of cryogenic containers used for whole-cortex MEG. (a) Placement of various MEG components relative to the cryogenic dewar; (b) Principles of the dewar operation. Reproduced with permission from (17).

Fig. 10: Schematic diagram of a typical MEG installation in a magnetically shielded room. Reproduced with permission from (17).

Fig. 11: Schematic diagram of a liver susceptometer. (a) SQUID gradiometer; (b) Superconducting magnet; (c) Bag filled with water to simulate the diamagnetism of human body tissue; (d) Patient on a bed which is vertically movable. Reproduced with permission from (197).

Fig. 12: Origin of the MEG signal. (a) Coronal section of the human brain. The neocortex is indicated by dark outer surface; (b) Pyramidal cells in the cortex have vertically oriented receptive areas (dendrites). Depolarization of the dendrites at the cortical surface due to

excitatory synaptic input results in Na^+ ions entering the cell producing a local current source and a current sink at the cell body, resulting in intracellular current flowing toward the cell body (arrow); (c) The cortex has numerous sulci and gyri resulting in currents flowing either tangentially or radially relative to the head surface; (d) Tangential currents will produce magnetic fields that are observable outside the head if modeled as a sphere; (e) Radial currents will not produce magnetic fields outside of the head if modeled as a sphere. Adapted with permission from (17).

Fig. 13: (a) Magnetic fields due to an equivalent current dipole source will exit and reenter the head that can be modeled as a spherical shaped conducting medium. (b) Calculation of the field magnitude (Bcoil) measured by a magnetometer coil due to a current dipole **q** at location $\mathbf{r_0}$ inside a sphere is given by the projection of the calculated vector field **B(r)** onto the direction normal to the surface area of the coil indicated by the unit vector **p**, such that $\text{Bcoil} = \mathbf{B(r)} \cdot \mathbf{p}$. The orientation of **q** is assumed to be tangential to the sphere surface. For gradiometer devices, the measured output of the gradiometer can be calculated as the difference between the field magnitudes calculated separately at each of the coils.

Fig. 14. (a) Topographic map (polar projection with nose upwards) of the magnetic field pattern recorded from 151 MEG channels over the scalp at a latency of 20 ms following stimulation of the right median nerve (average of 600 stimuli). White contours indicate outgoing fields and solid contours, ingoing fields. Arrow indicates direction of current flow below the scalp corresponding to the dipolar field pattern over the left hemisphere; (b) Location of a single ECD source corresponding to the magnetic field pattern shown in (a) indicated by white dot with

tail indicating direction of current flow superimposed on an axial slice of the individual's MRI. Location is in the hand region of the primary somatosensory cortex.

Fig. 15. Images of following response to flickering checkerboard stimulus at f = 17 Hz presented to the left or right visual field, using a whole-head MEG recordings and the synthetic aperture magnetometry (SAM) beamformer algorithm. The image shows increased source power as yellow (lighter) colored areas at the posterior portion of the brain, corresponding to increased power at 34 Hz (2f) in the primary visual cortex of the contralateral hemisphere. Unpublished data, figure courtesy of K. Singh.

Fig. 16. Dedicated system for fetal MEG measurement. (a) Schematic diagram of SQUID Array for Reproductive Assessment, (SARA) (48); (b) Layout of 151 sensing channels; (c) Example of flash evoked fMEG response, overlay of 151 SARA channels. The fetus with gestation age of 28 weeks was stimulated by 33 ms duration flashes of 625 nm wavelength light (185). Vertical dashed line corresponds to the flash stimulus onset. Adapted with permission from (198).

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